



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Art Unit: 3738

Pickford et al

Application number 10/501,538

Examiner: Christopher D

Prone

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Title: METAL IMPLANTS

**DECLARATION PURSUANT TO 37 CFR § 1.132**

1. I, Andrew Derek Turner, have extensive knowledge of and experience with chemistry, particularly inorganic chemistry, ion-exchange processes, and electrochemistry. I obtained a D Phil in chemistry from Oxford University, in the UK, in 1977. Since around 1981 I have worked on the applications of ion exchange and electrochemistry, initially as part of and later leading a team of scientists and engineers that at the outset formed a department within AEA Technology plc and then Accentus plc, based at Harwell in Oxfordshire, UK, and since 2003 I have provided consultancy services through a separate company, Alchimista Consulting Ltd, in Abingdon, Oxfordshire, UK. I am named as one of the inventors of the present application.
2. I have reviewed US patent US 5,185,075 (Rosenberg et al).
3. Neither Rosenberg et al, nor any of the prior art to my knowledge, discloses an implant with a metal substrate and an integral surface layer made by anodizing, in which the surface layer incorporates biocidal metal ions incorporated by ion exchange and in which the quantity of biocidal metal ions is such that the biocidal material is effective in suppressing infection after a surgical procedure.
4. Rosenberg et al's anodizing process aims at achieving a minimum leakage current, that is to say a good quality insulating dielectric oxide film, and this is achieved by applying the anodizing voltage until the current decays to a steady state, indicating the end of "age down", after which the oxide film becomes no more resistive with the passage of current (see col 7 lines 17, 30 and 43-46). The resulting films have leakage currents less than 25  $\mu\text{A}/\text{cm}^2$  (see col 11 lines 16-18). Such a good quality oxide film inevitably has poor ion exchange properties, as adsorption is limited to the exterior surface - with a saturation capacity equated to a monolayer of adsorbing ions. For silver, this saturation capacity would be equivalent to 0.3  $\mu\text{g}/\text{cm}^2$ .
5. Rosenberg et al's anodizing process uses a small quantity of silver nitrate solution added to the anodizing electrolyte in order to precipitate any halides that may be present; any excess silver nitrate forming silver phosphate (see col 12 lines 8-9 and 23) - which has a characteristic bright yellow coloration. The solubility of silver phosphate (as given by the Handbook of Chemistry and Physics "Rubber Handbook") is 0.00065 g/100 ml in water, equivalent to a concentration of Ag ions of 46.6  $\mu\text{M}$ . However, from data derived by Flett and Grunisholz (1951) on the solubility system  $\text{Ag}_2\text{O}/\text{P}_2\text{O}_5$  and  $\text{H}_2\text{O}$ , included in A Seidell's *Solubilities of inorganic and metal organic compounds*; a

*compilation of quantitative solubility data from the periodical literature*, it is clear that silver is significantly more soluble in phosphoric acid than water. I have estimated that at 5% H<sub>3</sub>PO<sub>4</sub> silver has a solubility of 0.16M, while at 25% H<sub>3</sub>PO<sub>4</sub>, this rises to 0.69M. I have also calculated that the pH equivalents of 5% and 25% acid are 1.10 and 0.74 respectively. The extremes of this range equate to proton concentrations of 0.08M to 0.18M. However, in every example the major ingredients of Rosenberg et al's anodizing electrolyte are aqueous phosphoric acid combined with an organic solvent, which complicates a more accurate estimate.

The pH at which titania adsorbs cations and anions equally (known at the pH of zero charge) is typically ~pH4.5, depending on method of fabrication. At pHs less than this titania will adsorb predominately anions, while above this it will adsorb primarily cations.

Rosenberg teaches that the silver addition is to remove halide ions (as an insoluble precipitate), as otherwise they can create imperfections in the anodized film. The assay of typical general purpose laboratory reagent grade phosphoric acid is <0.005% chloride. This equates to a maximum of 4 ppm chloride (5% acid) to 22ppm (25% acid). 22 ppm chloride equates to a concentration of 0.6x10<sup>-3</sup>M. Rosenberg specifies (column 5 lines 65-66) that silver should be added only in sparing amounts to remove the halides - implying that significant excess is not added, although column 12 line 23, allows for the detection of some silver phosphate formation. Even if a ten-fold excess of silver nitrate were added, the residual silver concentration would be only ~ 6x10<sup>-3</sup>M. In this case the ratio between the Ag ion concentration and the H ion concentration is in the range 1: 13 to 1: 30.

Thus in Rosenberg's process not only is the pH below the pH of zero charge, but the concentration of H ions is much greater than that of Ag ions. This high concentration of H ions would compete for any absorption sites for ion exchange on the titania, and would therefore tend to desorb any Ag ions that might be absorbed - indeed such acid solutions are typically used for removing cations absorbed on ion exchangers (known as elution).

6. I have also reviewed the processes described in the present patent application. The anodizing process is such as to produce a surface layer with significant ion exchange properties. After anodizing, the implant is rinsed, and then subjected to ion exchange treatment with 0.1 M silver nitrate. In this case the concentration of Ag ions is 0.1 M while the concentration of hydrogen ions is 1  $\mu$ M (i.e. pH6); and the ratio between the Ag ion concentration and the H ion concentration is 100,000 : 1. This pH is above the pH of zero charge, so it is this cationic concentration ratio that determines the driving force for Ag ions to be absorbed rather than desorbed, and the maximum number of adsorption sites that determine the saturation ion-exchange capacity. It is therefore apparent that this approach leads to a significant absorption of Ag ions and is vastly more effective in achieving absorption of Ag ions than would be the case in Rosenberg et al's process. Taking into account only the differences in the solutions, the concentration ratios driving the adsorption of biocidal ions achieved by the process of the present application would be between 1,300,000 and 3,000,000 times greater than that achievable using Rosenberg et al's solution; in practice the loading in Rosenberg et al's case would be even less (as the anodized layer is a good quality oxide (with a saturation loading capacity of only 0.3  $\mu$ g Ag/cm<sup>2</sup>) rather than a layer with significant ion exchange properties).

7. The implants produced by the process as specified in the present application are required to have a biocidal effect to suppress infection after the implant has been implanted in the human body. Silver ions are known to have such a biocidal effect. However silver ions are naturally present in human body fluids at levels that do not have any biocidal effect. On the other hand, if the silver ion concentration in the human body is too high, this can cause toxic symptoms or even, at slightly higher levels, cell death. So the requirement for the biocidal material to suppress infection inherently imposes very strict limits on the quantity of Ag ions present in the implant and on the rate at which they leach out into body fluids. For example the concentration of silver in the patient's plasma due to the implant should be at or above about 10 ppb to have any effect, but certainly must not exceed about 1000 ppb, while preferably being below about 300 ppb.

8. Experimental measurements have been made after anodizing by the process of the present application (i.e. forming a layer with ion exchange properties); the leakage current is around  $1.0 \text{ mA/cm}^2$ , which is over 40 times greater than the maximum value quoted in Rosenberg et al. This provides clear evidence of the difference in the anodized oxide layers.

9. Experimental measurements of the Ag loading in implants of the present invention have found that the silver loading is typically between about 3 and  $30 \mu\text{g/cm}^2$ , and such implants have been found to be effective in suppressing infection. The implants as specified in the present application have been found to produce the desired effect, such that the biocidal material is effective in suppressing infection after use of the implant in a surgical procedure. The implants of Rosenberg et al would have no effect in suppressing infection, as they contain such a minute quantity of Ag (over 1.3 million times less) that they would not have any detectable effect on the natural level of silver in the patient. This arises from the significant structural differences between the implants of the present application and those of Rosenberg, as explained above.

10. I declare that all of the above statements made of my own knowledge are true and all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. s.1001), and may jeopardize the validity of the application or any patent issuing thereon.

Date: 30<sup>th</sup> July 2007 By:  Andrew Derek Turner